

REVIEW ARTICLE

The role of IL-23 and the IL-23/T_H17 immune axis in the pathogenesis and treatment of psoriasis

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Abstract

Psoriasis is a chronic, immune-mediated disease affecting more than 100 million people worldwide and up to 2.2% of the UK population. The aetiology of psoriasis is thought to originate from an interplay of genetic, environmental, infectious and lifestyle factors. The manner in which genetic and environmental factors interact to contribute to the molecular disease mechanisms has remained elusive. However, the interleukin 23 (IL-23)/T-helper 17 (T_H17) immune axis has been identified as a major immune pathway in psoriasis disease pathogenesis. Central to this pathway is the cytokine IL-23, a heterodimer composed of a p40 subunit also found in IL-12 and a p19 subunit exclusive to IL-23. IL-23 is important for maintaining T_H17 responses, and levels of IL-23 are elevated in psoriatic skin compared with non-lesional skin. A number of agents that specifically inhibit IL-23p19 are currently in development for the treatment of moderate-to-severe plaque psoriasis, with recent clinical trials demonstrating efficacy with a good safety and tolerability profile. These data support the role of this cytokine in the pathogenesis of psoriasis. A better understanding of the IL-23/T_H17 immune axis is vital and will promote the development of additional targets for psoriasis and other inflammatory diseases that share similar genetic aetiology and pathogenetic pathways.

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Conflicts of interest

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Introduction

Psoriasis is a chronic, immune-mediated disease^{1–3} affecting approximately 100 million people worldwide⁴ and 2.2% of the UK population.⁵ Psoriasis affects men and women of all ages⁶ and can manifest in many different forms, the most common being psoriasis vulgaris (or plaque psoriasis).⁴ Plaque psoriasis is characterized by patches of erythema covered in a silvery-white scale,⁷ the result of rapid hyperproliferation and dysregulated differentiation of epidermal keratinocytes.⁸

The aetiology of psoriasis is multifactorial and includes a complex interplay of genetic, environmental, infectious and lifestyle factors.^{9,10} Genome-wide association studies have identified numerous psoriasis-associated gene loci,^{11–13} including the *HLA-Cw6* gene,¹⁴ specifically the HLA-class I allele, *HLA-C*06:02*,^{13,15} located within Psoriasis Susceptibility Locus 1 (*PSORS1* on 6p21.3).¹⁶ Polymorphisms located within this gene locus confer the highest risk of psoriasis (odds ratio [OR] 4.02–16.82).^{17,18} Gene loci outside the HLA region mostly represent common genetic variants with low effect sizes, including polymorphisms in the IL-23/T_H17 immune axis such as *IL12B* (OR 0.78–1.15) and *IL23R* (OR 0.87–1.10).^{11,13,17–21} Other variants, independent of *HLA-C*06:02*, are related to innate immune pathways, antigen presentation, and T-cell activation and differentiation.^{22–27} When combined with *HLA-C*06:02*, single-nucleotide polymorphisms in *IL23A*, *IL23R*, *IL12B*, *NFKB1* and *TNIP1* are associated with severe disease.¹⁷

Overall, most of the psoriasis-associated gene loci are related to the innate and/or adaptive immune system. However, as the majority of putative causal variants are located in noncoding regions,²⁸ and coupled with a complex genetic environment, it remains difficult to assign individual gene variants precise roles in the pathogenesis of, and susceptibility to, psoriasis.

Multiple inflammatory cell types are present in plaques, including dendritic cells (DCs), T cells and macrophages, which contribute to disease pathogenesis and drive keratinocyte proliferation.²⁹ T cells are known to be central to the pathogenesis of psoriasis; interfering with T-cell trafficking and cutaneous T-cell

recruitment improves psoriasis.^{30–32} Inhibition of CD8⁺ T-cell infiltration and activation into the epidermis prevented the development of psoriasis in a mouse model using human skin transplants.^{33,34} More specifically, CD4⁺ and CD8⁺ T cells with an interleukin-17 (IL-17) secretory phenotype (T-17 cells) are important contributors owing to their production of the pro-inflammatory cytokines IL-17, IL-22 and tumour necrosis factor (TNF).^{35,36} Also, a shift in the T-cell pool during psoriasis in which regulatory T cells (Tregs) begin expressing IL-17A has recently been identified.³⁷ Expression of the Treg master transcription factor Foxp3 is progressively lost, whereas expression of the T_H17 transcription factor retinoic acid receptor-related orphan receptor γ (ROR γ t), is increased by Tregs.³⁷ This process appears to be augmented by IL-23³⁷ and may be a contributing factor to the chronic inflammation seen in psoriasis. DCs are also important in the pathogenesis of psoriasis owing to their influence on T-cell activation and cytokine production. Myeloid DCs (CD11c⁺) are major producers of IL-23 in the skin,³⁸ Tip-DCs (a subset of CD11c⁺ DCs that express inducible nitric oxide synthase) are a source of TNF,³⁹ and plasmacytoid DCs produce high levels of type 1 interferon (IFN).^{40,41} CD163⁺-activated macrophages are also more abundant in psoriasis compared with normal skin⁴² and express products typical of classically activated macrophages, including IL-23p19 and IL-12/23p40.⁴² Although their exact role in the pathogenesis of psoriasis remains unclear, IL-17A-expressing neutrophils are known to aggregate in the epidermis, forming Munro's microabscesses in psoriatic lesions.⁴³ Finally, keratinocytes are a skin-specific source of IL-23 and, in health, maintain cutaneous immunity through activation of T-17 pathways.⁴⁴

It has been suggested that the localized activation and recruitment of inflammatory cells to plaques are the result of an autoimmune response in the skin.^{45,46} The human leucocyte antigen (HLA) class I allele, *HLA-C*06:02*, is the main risk allele in psoriasis.^{17,18} As HLA-class I molecules present peptide antigens from intracellular antigens to CD8⁺ T cells, a HLA-class I restricted autoimmune response must be directed against a particular target cell.⁴⁷ An unbiased analysis of epidermal CD8⁺ T-cell reactivity

unveiled an autoimmune response against melanocytes mediated by HLA-C*06:02 and identified ADAMTS-like protein 5 (ADAMTSL5) as a melanocyte autoantigen.⁴⁵ ADAMTSL5, expressed by epidermal melanocytes, activates CD8⁺ T cells in the epidermis and has been proposed as an explanation of why psoriasis manifests in the skin.⁴⁵ ADAMTSL5 stimulation increased production of IL-17A and IFN γ by peripheral blood mononuclear cells in 62% of patients with psoriasis.⁴⁵ Cathelicidin (LL-37) is another likely autoantigen.⁴⁸ LL-37 is a cationic peptide involved in antimicrobial defence and is known to stimulate T cells.⁴⁸ Complexed with nucleic material, LL-37 has been shown to activate the production of IFN by DCs through ligation of endosomal Toll-like receptors (TLRs).^{49,50} Circulating T cells specific to LL-37 were present in 46% of tested patients with psoriasis.⁴⁸ In addition, when complexed to bacterial DNA, IL-26 (a T-17 cell-derived cytokine) also activates DCs to produce IFN via ligation of TLRs.⁵¹ More recently, psoriatic T cells have been shown to recognize neolipid antigens generated by mast cell phospholipase delivered by exosomes and presented by CD1a.⁵²

The IL-23/T_H17 immune axis

When the immune system was initially considered dichotomous, being composed primarily of T_H1 and T_H2 cells, psoriasis was thought to involve a T_H1 response, driven by the cytokines IFN γ and IL-12.⁵³ However, clinical trials evaluating the efficacy of anti-IFN γ therapies for the treatment of psoriasis were not successful, indicating that IFN γ does not hold a bottleneck position

in the pathophysiology of psoriasis.⁵⁴ IL-12 is composed of two subunits, p35 and p40.⁵⁵ When increased expression of p40 was discovered in psoriatic lesions, this led to the initial conclusion that IL-12 expression was elevated in psoriasis.⁵⁶ However, when it was later shown that the p40 subunit of IL-12 is also found in IL-23,⁵⁷ Lee and colleagues were able to attribute the increased expression of p40 in psoriatic skin to IL-23³⁸ and not IL-12, as previously suggested.⁵⁶ As IL-23 is involved in the T_H17 axis,^{57,58} while IL-12 drives T_H1 cell development, the IL-23/T_H17 immune axis is now thought to be central to the pathogenesis of psoriasis. The main cytokines involved in psoriasis pathogenesis, IL-23, TNF and IL-17, can be subdivided into regulatory and effector cytokines based on their mode of action. IL-23 exerts regulatory effects on the maintenance of T_H17 cells, whereas IL-17 and TNF mediate effector functions of innate (TNF) and adaptive (TNF, IL-17) immune cells.

IL-23: a critical upstream cytokine in the pathogenesis of psoriasis

IL-23 is a key cytokine involved in protective immune responses to bacterial and fungal infections⁵⁹; however, dysregulated IL-23 production also promotes autoimmune inflammation.^{60,61} IL-23 was identified in 2000 as a heterodimer composed of the IL-12/23p40 subunit and a newly discovered p19 subunit that is exclusive to IL-23.⁵⁷ IL-23 signals through a heterodimeric receptor complex composed of two subunits, IL-23R and IL-12R β 1.⁶² This complex predominantly activates signal transducer and

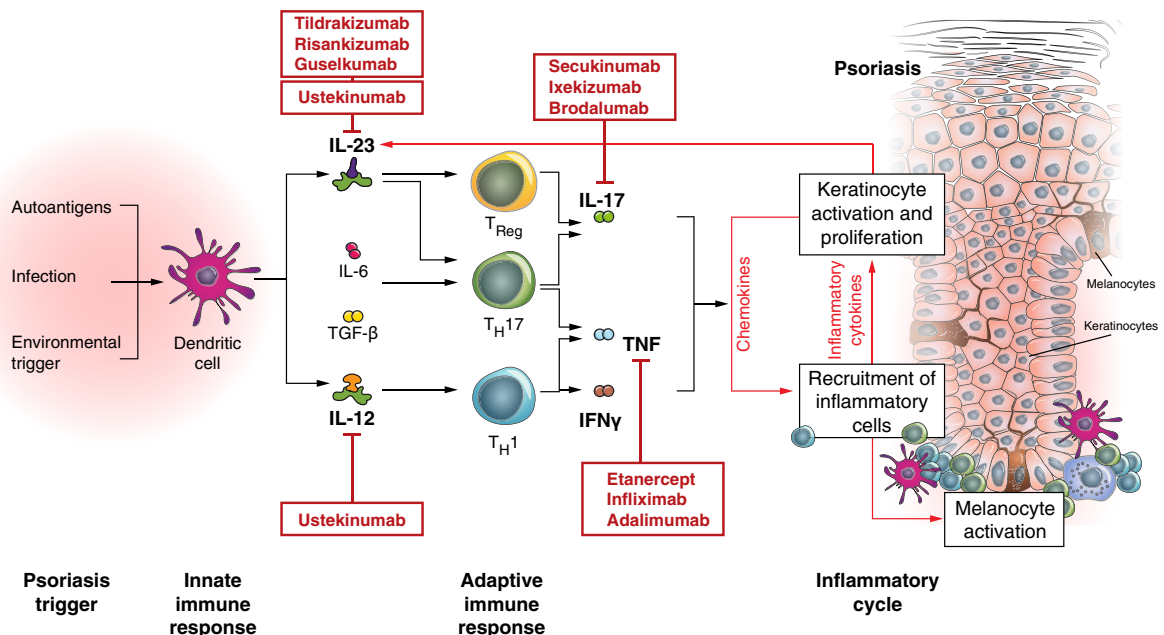


Figure 1 Pathogenesis of psoriasis and diversity of targeted therapies.^{29,37,64,149–151}

DC, dendritic cell; IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumour necrosis factor.

activator of transcription 3 (STAT3), leading to IL-23–dependent gene expression.⁶² IL-23 is an upstream regulatory cytokine that acts early in the inflammatory cascade in psoriasis (Fig. 1)^{58,63,64} to maintain the T_H17 cell phenotype⁶⁵ and is critical in the production of downstream effector cytokines, such as IL-17A, IL-17F and TNF (Table 1).^{63,65,66} It is important to note that IL-23 cannot directly promote T_H17 cell differentiation as the IL-23 receptor is not expressed on naïve T cells.^{61,65,67,68} IL-6 and transforming growth factor β (TGF- β) released by dermal DCs elicit ROR γ t-dependent differentiation of naïve T cells into T_H17 cells,^{67–70} and the phenotype is then maintained by IL-23.

Human studies and animal models of psoriasis have confirmed the critical role of IL-23 signalling in the pathogenesis of psoriasis. For example, IL-17A and IL-17F inductions were completely abolished in IL-23p19 knock-out mice,⁷¹ and intradermal injection of IL-23–induced skin changes was consistent with human psoriasis in wild-type mice.⁶³ In humans, expression of IL-23p19 messenger RNA is increased in psoriatic lesions compared with normal skin.³⁸ In patients with psoriasis, the IL-23 receptor is overexpressed on dermal DCs and epidermal Langerhans cells⁷²; whereas, in psoriatic lesions, IL-23 itself is overproduced by dermal DCs and keratinocytes.^{38,44,73} In mice, nociceptors interact with dermal DCs and induce the production of IL-23, which drives skin inflammation associated with psoriasis.⁷⁴

IL-17: a downstream effector cytokine

The IL-17 cytokine family consists of six isoforms termed IL-17 A–F.⁷⁵ Increased expression of IL-17A, E and F in psoriatic lesions has been described.^{76–78} T_H17 (CD4⁺) cells are a major source of IL-17A, although this cytokine can also be produced by CD8⁺ T cells and $\gamma\delta$ T cells,⁶⁴ natural killer T cells,^{79,80} mast cells and neutrophils.^{43,81} IL-17 is an effector cytokine downstream of IL-23⁶¹ that mediates psoriatic inflammation (Fig. 1).^{82–85} In health, T_H17 cells act to regulate protective immune responses, promote

microbial killing (via IL-26), and clear bacterial and fungal pathogens by inducing tissue inflammation.^{51,86} The IL-17 receptor is expressed on many cell types, including T cells, epithelial cells and fibroblasts.⁸⁶ IL-17 induces IL-17 receptor–dependent proliferation of keratinocytes and production of pro-inflammatory cytokines, including IL-1 β , IL-6 and TNF, and antimicrobial peptides, including β -defensin and matrix metalloproteinase 9.^{82–85,87} Blockade of either IL-17A or the IL-17 receptor has been shown to be an effective therapy in plaque psoriasis.^{88–90}

Therapeutic targeting in psoriasis

The evolution of biologics for the treatment of psoriasis has mirrored the evolving understanding of the immunopathogenesis of the disease (Fig. 1). Early treatment options centred on broad immunosuppression; however, as our understanding of the pathogenesis has improved, more-targeted therapies have become available.

TNF inhibitors

Efficacy of TNF blockade in psoriasis was identified in patients with inflammatory bowel disease (IBD) and psoriasis who were prescribed TNF inhibitors for the treatment of IBD.^{91,92} This observation initiated the clinical development of TNF inhibitors for psoriasis.^{93,94} TNF inhibitors currently approved for the treatment of psoriasis are etanercept,⁹⁵ adalimumab⁹⁶ and infliximab.⁹⁷ These agents have proven efficacy, but their broad mechanism of action is associated with safety issues, including an increase in the risk for severe bacterial and viral infections and potentially cancer.^{98,99} Concerns regarding the safety of TNF inhibition have driven a need for new, more-targeted biologics.

IL-17A inhibitors

The first IL-17A inhibitor for the treatment of moderate-to-severe plaque psoriasis, secukinumab, was approved for the

Table 1 Effects of IL-23 vs IL-17A in psoriasis

	IL-23	IL-17A
Cytokine type	Upstream cytokine	Effector (downstream) cytokine
Primary source	Activated monocytes and dendritic cells ^{145,146}	T _H 17 cells ^{146,147}
Primary target	T _H 17 cells ^{58,146}	Keratinocytes ¹⁴⁶
Role	Promotes maintenance of T _H 17 cells ^{37,103,147,148}	Key inflammatory effector cytokine that induces keratinocyte activation and proliferation and reduces differentiation ^{83,146}
Effect	Activation of T _H 17 cells to produce cytokines including IL-17A/F, IL-22, IL-26, IFN γ , and GM-CSF, which drives the inflammatory response ^{64,147}	Stimulates keratinocyte expression of antimicrobial peptides (LL-37 and β -defensins), pro-inflammatory cytokines (TNF, IL-1 β , IL-6) and chemokines (CXCL8–CXCL11, CCL20), which feed back into the pro-inflammatory cycle, resulting in a continued immunopathologic progression of psoriasis ^{145,149}
Potential consequences of blockade	Prolonged downregulation of immune activation, potential for a lower risk of AEs compared with IL-17 blockade	Short-term interference with effector immune mechanisms, potential for higher risk of AEs/infections compared with IL-23 blockade

AEs, adverse events; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LL-37, cathelicidin; T_H17, T-helper 17; TNF, tumour necrosis factor.

treatment of moderate-to-severe plaque psoriasis in 2015,¹⁰⁰ followed by ixekizumab in 2016.¹⁰¹ Both compounds have demonstrated strong efficacy with a fast onset of action. However, they require significant loading doses and frequent dosing to maintain responses.^{100,101} In addition, candidiasis occurred more frequently in patients with psoriasis receiving secukinumab compared with those taking etanercept, although the overall incidence was low.¹⁰² Increased susceptibility to infections has been identified in mice lacking IL-17 and the IL-17 receptor, but this effect has not been reported in humans who have mutations in the IL-23/T_H17 immune axis.¹⁰³ Targeting IL-17 and the IL-17 receptor has also been associated with exacerbated IBD in mice¹⁰⁴ and was ineffective in treating patients with moderate-to-severe Crohn's disease (CD).¹⁰⁵

Brodalumab, which targets the IL-17 receptor, has recently been approved for the treatment of moderate-to-severe plaque psoriasis.¹⁰⁶ In three phase 3 studies of brodalumab in moderate-to-severe plaque psoriasis (AMAGINE-1 [NCT01708590], AMAGINE-2 [NCT01708603], AMAGINE-3 [NCT01708629]), a $\geq 75\%$ improvement in the Psoriasis Area and Severity Index (PASI 75) was observed at Week 12 compared with baseline.^{107,108} An additional biologic, bimekizumab, an antibody targeting IL-17A, IL-17F, and the heterodimer IL-17A/F, is currently in development. A phase 1, first-in-human study of bimekizumab in patients with mild-to-moderate plaque psoriasis (NCT02529956), showed dose-dependent improvements in clinical features of plaque psoriasis, including PASI and Physician's Global Assessment scores, compared with placebo.¹⁰⁹

IL-12/23 inhibitors

Ustekinumab is currently the only approved drug that inhibits the IL-12/23p40 subunit, thus antagonizing both IL-12 and IL-23.¹¹⁰ Ustekinumab is generally considered safe and well-tolerated based on both clinical^{111,112} and longitudinal, real-world studies¹¹³ and long-term follow-up.¹¹⁴

Development of a second IL-12/23p40 antibody, briakinumab, was discontinued before all safety data were made available^{115,116}; some speculate that this decision was associated with cardiovascular safety concerns.¹¹⁷ However, meta-analyses and long-term follow-up of therapies targeting IL-12/23p40 show an overall reduced risk of cardiovascular events,^{118–120} so further data are needed to fully exclude a possible association between major cardiovascular events and the use of anti-IL-12/23 agents.

Development of biologics that specifically target IL-23 via IL-23p19, as opposed to the shared IL-12/23p40 subunit, may be of clinical benefit as IL-12 signalling is spared. A protective role for IL-12 in tumorigenesis has been suggested. In humans, IL-12 levels are significantly reduced in patients with breast cancer compared with healthy controls,¹²¹ and mutations in the *IL-12(p40)* gene lead to a higher risk of prostate cancer.¹²² IL-12 has also been shown to have a protective role, limiting skin inflammation by restricting the infiltration of IL-17-expressing $\gamma\delta$ T cells in the imiquimod mouse model of psoriasis.¹²³

IL-23 inhibitors in development

Three inhibitors specifically targeting IL-23p19 are currently in active development for the treatment of moderate-to-severe

Table 2 Comparison of efficacy for biologics targeting IL-23p19*

Characteristic	Tildrakizumab† 100 mg ¹²⁵	Tildrakizumab† 200 mg ¹²⁵	Guselkumab‡ 100 mg ^{126,127}	Risankizumab 180 mg ¹³⁰
Phase	Phase 3	Phase 3	Phase 3	Phase 2
Dosing schedule				
Initial	Weeks 0, 4	Weeks 0, 4	Weeks 0, 4	Week 0
Maintenance	q12w	q12w	q8w	q12w
Efficacy, %	Week 12	Week 12	Week 16	Week 12
PASI 75	61–64	62–66	86–91	88
PASI 90	35–39	35–37	70–73	79
PASI 100	12–14	12–14	34–37	48
PGA 0 or 1	55–58	59	84–85§	NR
Long-term efficacy, %	Week 28¶	Week 28¶	Week 24	Week 36
PASI 75	73–80	73–82	89–91	88
PGA 0 or 1	65–66	69	84§	NR

*Data are not from head-to-head comparisons.

†Data from reSURFACE1 and reSURFACE2 trials.

‡Data from VOYAGE 1 and VOYAGE 2 trials.

§IGA 0 or 1 reported.

¶Responder analysis includes only PASI 75 responders at Week 16.

IGA, investigator global assessment; IL, interleukin; NR, not reported; PASI, Psoriasis Area Severity Index; PGA, Physician's Global Assessment; q8w, every 8 weeks; q12w, every 12 weeks.

psoriasis (Table 2): tildrakizumab, guselkumab and risankizumab. A further antibody, LY3074828 (mirikizumab), is now entering phase 2 development.¹²⁴

Two phase 3 studies of tildrakizumab have been completed: reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754). These studies demonstrated the efficacy of tildrakizumab at Week 12 compared with placebo (reSURFACE 1 and 2) or etanercept (reSURFACE 2 only) (PASI 75: reSURFACE 1: 200 mg 62%, 100 mg 64%, placebo 6%; reSURFACE 2: 200 mg 66%, 100 mg 61%, placebo 6%, etanercept 48%; $P \leq 0.001$ in all comparisons).¹²⁵ Of the patients who responded

to tildrakizumab 200 mg at Week 28 (achieved PASI 75 response: reSURFACE 1: 200 mg 82%; reSURFACE 2: 200 mg 73%), 94% and 97% of patients maintained the response at Week 64 (reSURFACE 1) and Week 52 (reSURFACE 2), respectively.¹²⁵

The results from the guselkumab phase 3 trials, VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT02207244), showed efficacy in treating moderate-to-severe psoriasis compared with placebo and adalimumab at Week 16 (PASI 90 [co-primary endpoint]: VOYAGE 1: guselkumab 73%, adalimumab 50%, placebo 3%; VOYAGE 2: guselkumab 70%, adalimumab 47%, placebo, 2%), Week 24 (VOYAGE 1: guselkumab 80%, adalimumab

Table 3 Most common adverse events and adverse events of special interest for biologics targeting IL-23p19*

Characteristic	Tildrakizumab† 100 mg ¹²⁵	Tildrakizumab† 200 mg ¹²⁵	Guselkumab‡ 100 mg ^{126,127}	Risankizumab 180 mg ¹³⁰
Phase	Phase 3	Phase 3	Phase 3	Phase 2
Dosing schedule				
Initial	Weeks 0, 4	Weeks 0, 4	Weeks 0, 4	Week 0
Maintenance	q12w	q12w	q8w/q12w	q12w
Safety, %	Weeks 0–12	Weeks 0–12	Weeks 0–16	Weeks 0–24
AE	44–47	42–49	48–52	57
SAE	1–2	2–3	2	2
Severe infections	<1	<1	<1§	NR
Malignancies	<1	<1	0	NR
MACE	<1§	0¶	<1**	NR
Drug-related hypersensitivity reactions	<1	<1	NR	NR
Long-term safety, %	Weeks 12–28	Weeks 12–28	Weeks 16–48††	NR
AE	44–46	40–45	65	NR
SAE	2–3	2	3	NR
Severe infections	≤1	≤1	1§	NR
Malignancies	<1	≤1	0	NR
MACE	0	0	0	NR

*Data are not from head-to-head comparisons.

†Data from reSURFACE1 and reSURFACE2 trials.

‡Data from VOYAGE 1 and VOYAGE 2 trials.

§Serious infections.

¶Includes non-fatal myocardial infarction, non-fatal stroke and CV deaths that are confirmed as ‘cardiovascular’ or ‘sudden’.

**Includes sudden cardiac death, myocardial infarction and stroke.

††VOYAGE 1 trial only.

AE, adverse event; IL, interleukin; MACE, major adverse cardiac event; NA, not available; NR, not reported; Q8w, every 8 weeks; q12w, every 12 weeks; SAE, serious adverse event.

Table 4 Additional research needs

To fully understand the mechanism of action of IL-23 and IL-17 blockade in psoriasis and other chronic inflammatory diseases, there is a need for research that explores:
• Cellular sources of IL-23 and IL-17 in psoriasis and conditions for the expression of the IL-23R and the IL-17R
• The effect of IL-23 inhibition on T _H 17 cells in the skin and/or lymph nodes, and the downstream effects on cytokine profile in psoriatic lesions
• The role of IL-23 inhibition in modulating the immune response and the effect on cytokines other than IL-17
• Contribution of innate immunity (e.g. recruitment of neutrophils to lesions)
• Genetic differences between responders and non-responders to IL-17 or IL-23 inhibition
• Autoantigens and triggers in psoriasis, including environmental triggers

IL, interleukin; T_H17, T-helper 17.

53%; VOYAGE 2: guselkumab 75%, adalimumab 55%), and over a 1-year period (VOYAGE 1 only: Week 48, guselkumab 76%, adalimumab 48%; $P < 0.001$ in all comparisons).^{126–128}

Phase 1 data on risankizumab in moderate-to-severe chronic plaque psoriasis (NCT01577550) reveal significant improvements in the proportion of patients achieving PASI 75 at Week 12 (PASI 75: risankizumab 87%, placebo 0%, $P < 0.001$) and Week 24 (risankizumab 71%, placebo 13%, $P = 0.009$) compared with baseline.¹²⁹ In addition, a phase 2 study (NCT02054481) demonstrated superior clinical responses compared with ustekinumab at Week 12 (PASI 75: risankizumab 180 mg 88%, ustekinumab 45/90 mg 73%) and at Week 36 (risankizumab 180 mg 88%, ustekinumab 45/90 mg 55%).¹³⁰

Overall, preliminary data suggest that anti-IL-23p19 agents have a favourable safety profile (Table 3). As the p19 subunit is exclusive to IL-23, whereas the p40 subunit is common to both IL-12 and IL-23, therapies that selectively target IL-23p19 should avoid unnecessary effects associated with IL-12/23p40 inhibition by sparing the function of IL-12. This is supported by animal data in which IL-12-deficient mice are susceptible to chemical carcinogenesis, whereas IL-23-deficient mice are resistant.¹³¹ In patients with solid tumours, 1-year survival was significantly greater in patients with elevated serum levels of IL-12.¹³² However, when targeting IL-12/23p40, it is not possible to attribute individual adverse events to specific inhibition of either IL-12 or IL-23. The relative contributions of each subunit to the safety profile will become apparent as more data from selective IL-23 inhibitors become available. To date, IL-23p19 inhibitors currently in development have not encountered signals for opportunistic infections, malignancy or worsening of IBD or CD.^{129,133,134}

Dosing regimens

Comparison of treatment regimens across clinical trials suggests that biologics blocking effector cytokines may require more frequent dosing compared with biologics that block upstream cytokines. Approved agents that block IL-17 require large loading doses with frequent administration within the first 4–12 weeks (secukinumab loading dose of 300 mg administered weekly for 4 weeks; ixekizumab loading dose of 160 mg administered once and 80 mg administered every 2 weeks for 12 weeks), with a reduction to one dose every 4 weeks for response maintenance.^{100,101} These dosing intervals correspond to one to two serum half-lives.^{100,101} In comparison, biologics that target IL-23 require less loading and allow a greater dosing interval for response maintenance (Table 2), corresponding to approximately four serum half-lives.^{129,135,136} This is probably due to differing pharmacokinetic properties and antibody affinity for IL-23p19^{129,135,136} but might also suggest that blocking regulatory upstream cytokines may have a longer lasting effect on the pathogenic immune response in psoriasis compared with blocking effector cytokines. We propose that neutralizing IL-23 prevents the maintenance of the ongoing pathogenic T_H17 response

without affecting the induction of T_H17 differentiation, which depends on IL-6 and TGF- β .^{65,67–70}

IL-23 inhibition in other inflammatory diseases

The aetiologies of psoriasis, psoriatic arthritis and CD share several candidate genes and common pathogenetic pathways, which is not surprising considering the clinical overlap of the disorders.^{26,137–140} Mutations in genes upregulated in these conditions, including *IL23R*, affect the IL-23/T_H17 immune axis,^{139,141} suggesting anti-IL-23 agents may have potential as treatments for CD, psoriatic arthritis and other genetically related disorders. For example, the TNF inhibitors adalimumab and infliximab are approved for the treatment of psoriasis and CD,^{96,97} and ustekinumab was recently approved for the treatment of CD.¹¹⁰ In addition, several anti-IL-23 agents are undergoing clinical development in psoriatic arthritis^{142,143} and CD.¹⁴⁴

Conclusions

There is robust evidence that the IL-23/T_H17 immune axis is a key driver of psoriatic inflammation, which has led to the development of biologics that specifically target key elements of this pathway. Although there are still gaps in our understanding (Table 4), IL-23 is now acknowledged to have a critical role in this pathway and is required for the maintenance of inflammatory T_H17 cells. Early indications from clinical trials support the use of IL-23p19-specific inhibitors as a viable treatment option that may bring additional benefits to patients with plaque psoriasis.

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